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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,602	11/16/2000	David William Holden	RPMS 101 CON(3)	4552

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SMP.

Office Action Summary	Application No.	Applicant(s)	
	09/714,602	HOLDEN, DAVID WILLIAM	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,57-73 and 76-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,57-73 and 76-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/01/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Petition Decision Copy*.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/24/2004, in which claim 57 was amended and in which claim 86 was cancelled. Claims 3, 57-73 and 76-78 are pending in the instant application.

Response to Amendment

Any rejection of record in the previous office action mailed on 11/17/2003 that is not addressed herein is withdrawn. This office action is not final as there are new grounds of rejection made herein that were not necessitated by applicants' amendment of the claims in the response filed 5/24/2004. For example, the examiner was mistaken in the previous office action in stating that the new, broad claims submitted in the preliminary amendment on the filing date of the instant application are not new matter. As indicated on the attached courtesy copy of the petition decision concerning priority in the instant application, MPEP 601.01(a) states that if an amendment is filed on the same day that the application filed under 37 CFR 1.53(b) is filed and is referred to in the original oath or declaration filed with or after the application, it constitutes a part of the original application papers and the question of new matter is not considered. It is suggested that applicant submit a new oath or declaration referring specifically to the preliminary amendment in order to overcome the following new matter rejection.

Alternatively, the issues of new matter and the denial of priority to the parent applications for the current claims could be resolved by amending the claims to clearly indicate that the plurality of mutant microorganisms are generated by insertional inactivation of genes within the genome of the microorganism. Applicant's arguments in

response to the previous office action will be addressed in more detail below, but it appears that applicants may believe that the examiner was directing his arguments to the lack of language in the claims regarding transposons or "transposon-like elements". In fact, this is not the case.

The examiner understands the term "transposon-like elements" to broadly encompass other types of insertional activation, including the alternative methodologies cited in applicants' response as being supported in the instant application (i.e. insertional inactivation of genes by insertion-duplication mutagenesis, random plasmid integration in fungi, use of Ty elements or ribosomal DNA for insertional mutagenesis in yeast; see pages 11-12 of the instant specification). As currently written, the claimed method embraces any method for generating mutants of a microorganism where each mutant has a unique sequence that satisfies the limitation of being a marker sequence for that mutant. For example, , the claims encompass embodiments where mutations are introduced into the genome of the microorganism by chemical mutagenesis, wherein the unique mutation present in the genome of the individual mutants could be detected as a unique marker for that mutant. Alternatively, mutants could be generated by transforming microorganisms with episomal vectors encoding a unique gene suppression element (e.g. antisense, siRNA, ribozymes) having a unique sequence for each mutant. Expression of the suppression element would then generate a mutant cell having altered phenotype. It is these types of embodiments, where gene suppression is not mediated by insertional inactivation, which are not supported by the originally filed specification.

Petition Under 37 CFR 1.181/Priority

Receipt is acknowledged of a petition filed on 6/28/2004 concerning the denial of priority to parent applications made by the examiner in the office action mailed 11/17/2003. As indicated on the attached courtesy copy of the petition decision, the petition has been denied (the official copy of the decision has been mailed separately). For reasons of record in the previous office action, denial of priority for the instant application to applications 09/201,945 and 08/637,759 is maintained. The date of priority for the invention recited in the instant claims is the filing date of the instant application, 16 November 2000.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a).

As indicated above, the instant application is not a continuation application of 09/201,945 due to the new subject matter introduced by the preliminary amendment filed on the filing date (11/16/2000). Therefore, applicant cannot rely upon a declaration filed for application 08/637,759, upon which application 09/201,945 was a continuation. It is necessary for applicant to submit a new declaration that addresses the new methodology introduced by the preliminary amendment filed 11/16/2000. Such a declaration, referring

specifically to the preliminary amendment of the claims filed 11/16/2000, will obviate the new matter portion of the written description rejection made below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 57-73, 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection in that it comprises language directed to NEW MATTER issues. It also incorporates the grounds of rejection made in the previous office action concerning a lack of description for the broadly claimed genus of methods.**

Each of the rejected claims is directed to a method of identifying a mutant microorganism having a reduced adaptation to a particular environment wherein a plurality of microorganisms is provided and wherein each mutant microorganism comprises a different marker sequence. The plurality of mutant microorganisms is introduced into a particular environment and those microorganisms that are able to do so are allowed to grow in that environment for some time. Subsequently, microorganisms are recovered from the environment and mutant microorganisms having a reduced capability to adapt to the environment are selected by comparing the marker sequences

within the retrieved microorganisms, if any, to those originally put into the particular environment. The rejected claims encompass any methodology for generating the mutant microorganisms (e.g. chemical mutagenesis, episomal suppression of gene expression), so long as the mutant microorganism comprises a unique marker sequence. In contrast, the originally filed specification and claims are entirely directed to insertional inactivation of genes within the genome of the microorganism. Therefore, there is no literal support in the originally filed specification or claims for the broad genus of methods encompassed by the instant claims. Therefore, the instant claims comprise impermissible NEW MATTER.

Should applicant overcome the grounds for rejection on the basis of new matter by filing a new oath or declaration referring to the 11/16/2000 preliminary amendment, the rejected claims will still lack sufficient description of the broadly claimed genus of methods. Each of the claims is drawn to a method of identifying a microorganism having a reduced adaptation to a particular environment comprising: (a) a plurality of microorganisms wherein each contains a different marker sequence; (b) introducing the plurality of microorganisms in a particular environment and allowing those that are able to grow in that environment to do so; (d) retrieving the ones that are able to grow from the particular environment; and (d) selecting an individual microorganism having a reduced capacity to proliferate in the particular environment by comparing marker sequences in the nucleic acid present in the retrieved microorganisms, if any, to the original marker sequences put into the particular environment. The rejected claims encompass embodiments wherein the original microorganisms are not mutants, or are mutants generated by an undefined method, where the nature of the tag sequence is not

defined. Nor is the nature of the marker sequence defined. Thus, the rejected claims encompass a number of different sequence markers introduced into the microorganisms in different ways and used to determine the identity of a microorganism having a reduced capacity to adapt to a particular environment.

The instant specification is explicitly limited to methods of identifying genes where the methods comprise insertional inactivation of genes within the genome of a target microorganism (e.g. a pathogen) with transposon elements (or "transposon-like" elements) comprising a unique nucleic acid tag sequence. In these methods, a plurality of mutants having unique tag sequences are introduced into a particular environment (e.g. a multicellular organism) and grown for some period of time. Surviving microorganisms are harvested from the particular environment and the unique nucleic acid "tags" obtained from the surviving microorganisms probed with a bank of the unique nucleic acid tags for all of the microorganisms introduced into the particular environment. Those tags from the bank of unique tags that do not hybridize with those present in the genomes of the surviving microorganisms correspond to insertion events into genes essential for viability of the microorganism in the particular environment. Thus, the methods result in the identification of microorganisms having a reduced adaptation to a particular environment.

The specification does not describe any other approach for providing microorganisms, mutant or otherwise, having unique sequence tags or markers for use in the claimed methods. The specification describes no other means of "selecting by comparison" of microorganisms having a reduced ability to adapt to a particular environment than comparison of nucleic acid tags present within transposable elements from surviving microorganisms to those present in the microorganisms prior to their

insertion into the particular environment. The specification does not provide *any* description of what other methods embraced by the claims might look like (i.e. what the methods steps would be). Therefore, the skilled artisan would not have been able to envision a sufficient number of different methods embraced by the rejected claims to describe the broadly claimed genus of such methods of identifying a microorganism have a reduced adaptation to a particular environment.

Claims 3, 57-73, 76-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein (1) a plurality of microorganisms is provided wherein each of the microorganisms is independently mutated by the insertional inactivation of a gene with a nucleic acid comprising a unique marker sequence so that each mutant contains a different marker sequence, and (2) the mutant microorganism having a reduced ability to adapt to a particular environment is selected by (i) comparison of the different unique marker sequences obtained from microorganisms that are able to grow in the particular environment to the collection of unique marker sequences present in the plurality of microorganisms introduced into the particular environment, and (ii) the mutant microorganism is identified based upon its lack of a unique marker sequence obtained from the population of microorganisms able to grow in the particular environment, does not reasonably provide enablement for methods that do not comprise these elements. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the previous office action.**

Response to Arguments/112 1st Rejections

Applicant's arguments filed 5/24/2004 have been fully considered but they are not persuasive. With regard to the written description rejection of record, the response essentially argues:

1) amendment of part (d) obviates the part of the rejection directed to the use of any marker sequences present in the microorganisms retrieved from the particular environment,

2) it is not important to the operation of the method how the mutant microorganisms are generated provided they have different marker sequences that one can use to track the fate of the mutant microorganism in the particular environment,

3) the term "marker sequence" is self-defining and the word "tag" is not used in the claims,

4) the specification does describe other approaches for generating mutant microorganisms comprising different marker sequences (e.g. at pages 11-12),

5) page 13, lines 17-18 teach that transposons may be used "or other DNA sequences",

6) it is well established that one need not describe in detail that which is known to those in the field in order to meet the written description requirement,

7) several post-filing references describe the claimed invention where marker sequences are used to "bar code" mutant strains of microorganisms and follow their fate in different environments (e.g. Hensel et al, Shoemaker et al, Winzeler et al, WO 01/53532, Lum et al), and

8) Hensel et al, which teaches the work described in the instant specification, is the seminal work in the field describing marker sequences to mark or "bar code" mutant strains.

With regard to the rejection of the claims on the grounds of a lack of enablement for the full, broad scope of methods recited in the rejected claims, the response essentially argues:

1) the nature of the invention is complex, but the level of skill in the art is high,

2) the amended claims clearly provide a correlation between the marker sequences recovered and those originally introduced to the particular environment,

3) the embodiments claimed are described in the specification,

4) the specification does describe different mutants containing different marker sequences made other than by transposons as well as methods of identifying mutant microorganisms that are not adapted to survive in a particular environment,

5) there are clear working examples of the method claimed and the skilled artisan has not practical difficulty in carrying out the invention as claimed,

6) post-filing art demonstrates the instant invention is enabled,

7) it would not have been unpredictable for the skilled artisan to practice the claimed methods, and

8) it is important that the examiner appreciate the very important contribution to the art made by the inventors as defined in the claims.

With regard to applicants' amendment of step (d) of the rejected claims, the amended claims clearly link the marker sequences obtained from the retrieved microorganisms, if any, to those present in the microorganisms originally put into the particular environment. Thus, the grounds of rejection pertaining to step (d) and a lack of correlation between the marker sequences of step (c) and step (a) are withdrawn.

However, the issue of whether there is any support for embodiments that do not feature gene inactivation by insertion of a "transposon-like" element remains. As indicated above, the examiner interprets the term "transposon-like" element to encompass nucleic acid constructs used in the various insertional inactivation methods described in the instant specification. The portions of the specification cited in applicant's response all are directed to different methods of gene inactivation via insertion of a heterologous nucleic acid sequence such that the gene is inactivated (e.g. plasmid insertion and duplication, Ty elements, etc.). The issue is whether there is sufficient support for embodiments that do not involve insertional inactivation of genes (e.g. a plurality of "natural" mutants of different genes in a microorganism wherein the different mutant sequences are themselves "markers" that can be compared before and after growth in a particular environment). The post-filing art appear to be all directed to methodologies where the individual mutants are generated by insertional mutagenesis of genes to incorporate the unique marker sequences. Therefore, the post-filing art does not support enablement or description for any embodiments that do not feature the insertional inactivation of target genes. Finally, the examiner does appreciate the contribution of "bar coding" mutants as is taught in the instant specification over the prior art with regard to identification of mutants that do not thrive in a particular environment. The fact

remains, though, that there is insufficient descriptive support or guidance for those embodiments that do not feature insertional gene inactivation to generate the claimed mutants.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As noted above, the instant claims are accorded priority only to the filing date of the instant application (11/16/2000). The specific embodiments taught by Hensel et al anticipate the instant claims, which are broader in scope than what is described in the instant specification.

Claims 57-60, 64-66, 69-73, 76 & 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Hensel et al (Science, 21 July 1995, Vol. 269, pages 400-403; see the entire document). **This is a new rejection.**

Hensel et al teach a system for insertional mutagenesis that uses transposons carrying unique DNA sequences (i.e. "tags") to inactivate essential genes in bacteria. When applied to a murine model of typhoid fever caused by *Salmonella typhimurium*, mutants with attenuated virulence were revealed by the use of tags that were present in the inoculum but not in bacteria recovered from infected mice (e.g. Abstract; Figure 1). Unique marker sequences were recovered from bacteria retrieved from the infected mice

and amplified using DNA amplification techniques (e.g. Figure 1) and compared to the marker sequences present in the inoculums (e.g. Figure 2). Various virulence genes were identified from those clones with a reduced capacity for growth upon inoculation into the mouse (e.g. Table 1).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
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